



September 19, 2017

BY ELECTRONIC MAIL

Dr. Tala R. Henry
Director, Risk Assessment Division
Office of Pollution Prevention and Toxics
US Environmental Protection Agency
1200 Pennsylvania Avenue, N. W.
Mail Code: 7403M
Washington, DC 20460

RE: Risk Evaluation Scoping Efforts under the Toxic Substances Control Act (TSCA) for
1,4-Dioxane, Docket No. EPA-HQ-OPPT-2016-0723

Dear Dr. Henry

The American Chemistry Council's (ACC) 1,4-Dioxane Panel appreciates the opportunity to submit information pertinent to the Office of Pollution Prevention and Toxics' (OPPT) problem formulation for the risk evaluation of 1,4-dioxane under TSCA. The ACC Panel includes companies with a variety of perspectives on 1,4-dioxane, but with a common interest in the assessment of health effects to be included in OPPT's evaluation. The problem formulation step will frame the scientific issues that will be the focus of the risk evaluation. One of the critical elements of the evaluation of a chemical like 1,4-dioxane is the determination of the likely operative mode of action (MOA) of carcinogenesis. It will be important, therefore, that - as part of its consideration of best available science and weight of the evidence (WOE) required by TSCA § 26 - OPPT conduct a comprehensive evaluation of the carcinogenic MOA of 1,4-dioxane. This is particularly true in light of recently published information on the histopathology available from the cancer bioassays for the chemical.¹

As part of the Agency's problem formulation for 1,4-dioxane, OPPT is encouraged to use the WOE method for scoring confidence in the supporting data to improve the scientific justification for the MOA used in characterizing hazards and selecting dose-response extrapolation methods for

¹ Dourson ML *et al.* Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1,4-dioxane. *Reg Toxicol Pharma* 88: 45-55 (2017). Available at <http://www.sciencedirect.com/science/article/pii/S0273230017300429>.



specific chemicals described in Becker *et al.* (2017).² This method provides a systematic and explicit approach for –

- evaluating a chemical dataset using hypothesized MOAs and the evolved Bradford Hill causal considerations,³ and
- deriving an overall confidence score for each hypothesized MOA.

This quantitative-scoring method allows OPPT to enhance transparency and communication of the relative extent of the available evidence for an MOA to risk assessment experts, less experienced practitioners, risk managers, and the public. It enables a side-by-side comparison of numerical WOE confidence scores for each MOA, and the determination of which MOA is more likely to be operative.

To illustrate this method, we have developed a case example based on data of rodent liver tumors induced by 1,4-dioxane (enclosed). This example uses data and lines of evidence from published articles, and relies on the authors' evaluation of the quality of the empirical evidence. Two hypothesized MOAs were considered: 1) induction of rodent liver tumors via a mutagenic MOA; and 2) induction of rodent liver tumors via a cytotoxicity MOA. The quantitative MOA WOE confidence scoring results of this case example indicate:

- It is highly unlikely that 1,4-dioxane induces rodent liver tumors via a mutagenic MOA;
- Cytotoxicity and sustained regenerative cellular proliferation is the likely operative MOA for induction of liver tumors in rodents by 1,4-dioxane;
- Significant mechanistic data are available to support a non-linear, non-mutagenic MOA for rodent liver tumors;
- Based on the comparison of quantitative MOA WOE confidence scores, there is strong scientific support for using a threshold extrapolation approach for evaluating cancer risks; and
- In contrast, scientific justification is lacking in support of a linear, no threshold extrapolation method for evaluating cancer risks.

The 1,4-Dioxane Panel welcomes the opportunity to review this information with you and your staff. Please do not hesitate to contact me at srisotto@americanchemistry or at 202-249-6727

² Becker RA *et al.* 2017. Quantitative weight of evidence to assess confidence in potential modes of action. *Reg Toxicol Pharma.* 86: 205-220 (2017). Available at <http://www.sciencedirect.com/science/article/pii/S0273230017300387>.

³ These considerations include biological plausibility, essentiality, dose-response concordance, consistency, and analogy.



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if you have any questions on the confidence scoring method for comparing MOAs or its application to 1,4-dioxane.

Sincerely

Steve Risotto

Stephen P. Risotto
Senior Director
Chemical Products and Technology Division

Enclosure: Identifying the Likely Operative Mode of Action for 1,4-Dioxane Induced Rodent Liver Tumors (September 14, 2017)

